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Express Mail No. **EV 346 810 507 US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: Denis JACOBY

Confirmation No. 9181

Application No: 10/688,297

Group Art Unit: 1625

Filing Date: October 17, 2003

Examiner:

For: CATALYTIC SYSTEM FOR ALDOL  
REACTIONS

Atty. Docket No.: 81455-5510

**SUBMISSION OF CERTIFIED PRIORITY DOCUMENT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Sir:

Applicant have claimed priority under 35 U.S.C. § 119 of PCT Application No. PCT/IB01/00902 filed May 22, 2001. In support of this claim, a certified copy of said application is submitted herewith.

No fee or certification is believed to be due for this submission. Should any fees be required, however, please charge such fees to Winston & Strawn LLP Deposit Account No. 50-1814.

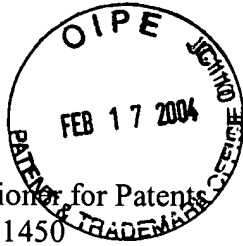
Respectfully submitted,

Date: 2/17/04

  
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Enclosures



EXPRESS MAIL LIST

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The following items listed below are being filed herewith with the USPTO on **February 17, 2004**

Express Mail No. <b>EV 346 810 507US</b>		
Attorney Docket No.	Appln. Serial No.	Items - Documents filed on <b>February 17, 2004</b>
81455-5510	10/688,297	<b>Submission Of Certified Priority DocumentPCT/IB01/00902</b>

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**PATENT COOPERATION TREATY (PCT)  
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International Application No. } **PCT/IB01/00902**  
Demande internationale n° }

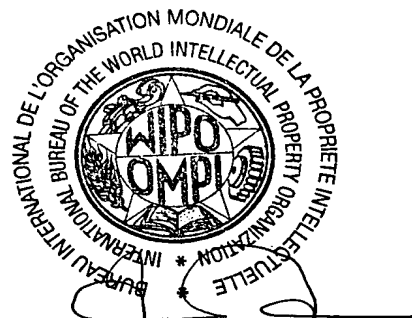
International Filing Date } **22 May 2001**  
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Geneva/Genève,

**17 September 2003  
(17.09.03)**

**International Bureau of the  
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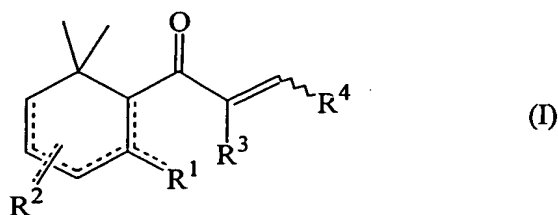
**J.-L. Baron**

**Head, PCT Receiving Office Section  
Chef de la section "office récepteur du PCT"**

## CATALYTIC ALDOL CONDENSATIONS

Technical field

The present invention relates to the field of organic synthesis and more precisely to a synthesis of enones (I) by the catalyzed aldol condensation of a saturated or unsaturated cyclohexylethanone derivative with acetaldehyde, without the pre-formation of an enolate



wherein the wavy line indicates that the stereochemistry of the C=C double bond is not defined and the dotted lines indicate a single or a double bond, R<sup>1</sup> represents a hydrogen atom or a methyl, methylene or ethyl group, R<sup>2</sup> represents a hydrogen or a methyl or ethyl group, R<sup>3</sup> represents a hydrogen atom or a methyl group and R<sup>4</sup> represents a hydrogen atom or a C<sub>1</sub> to C<sub>4</sub> linear or branched alkyl or alkenyl group.

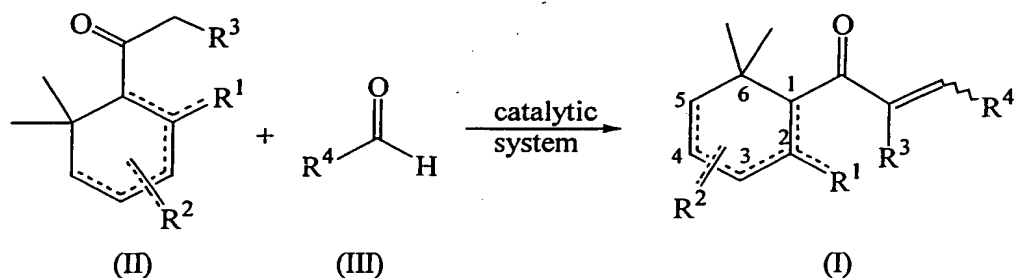
Prior art

To the best of our knowledge, until now, only one process is known to allow the preparation of compounds of formula (I) on a large scale. Said process, which is described in Ayyar *et al. J. Chem. Soc., Prekin Trans. I*, 1975, 17, 1727, suffers of the drawback of using a stoichiometric amount of a strong base such as the N-methylanilinomagnesium bromide for the formation of an enolate. Strong bases such as an amide anion have the inconvenience of being expensive and difficult to manipulate, therefore a process implying large amounts of said base does not represent the best solution for the preparation of compounds (I).

# Description of the invention

In order to overcome the problems aforementioned, the present invention relates to a new, single step, catalyzed aldol condensation process, which does not require the pre-  
5 formation of an enolate, aimed at the synthesis of a compound (I) according to Scheme 1:

Scheme 1



10

wherein the wavy line indicates that the stereochemistry of the C=C double bond is not defined and the dotted lines indicate a single or a double bond;

R<sup>1</sup> represents a hydrogen atom or a methyl, methylene or ethyl group;

R<sup>2</sup> represents a hydrogen atom or a methyl or ethyl group;

15 R<sup>3</sup> represents a hydrogen atom or a methyl group; and

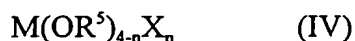
R<sup>4</sup> represents a hydrogen atom or a C<sub>1</sub> to C<sub>4</sub> linear or branched alkyl or alkenyl group.

Preferably, R<sup>1</sup> represents a methyl or methylene group, R<sup>2</sup> represents a hydrogen or a methyl group, R<sup>3</sup> represents a hydrogen atom and R<sup>4</sup> represents a methyl group.

Particularly, preferred starting ketones (II) are 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1-ethanone, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-1-ethanone, 1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-1-ethanone, 1-(2,6,6-trimethyl-4-cyclohexen-1-yl)-1-ethanone, 1-(6,6-dimethyl-2-methylene-1-cyclohexyl)-1-ethanone, 1-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-1-ethanone and 1-(2,6,6-trimethyl-5-methylene-1-cyclohexyl)-1-ethanone.  
20

As shown in Scheme 1, the process of the invention needs a catalytic system. By  
25 catalytic system it is intended a mixture of a metal complex and of a co-ingredient, said metal complex being used in substoichiometric or catalytic amounts relative to the starting aldehyde.

The metal complex has a general formula:



wherein M is a tetravalent metal cation selected from the group consisting of Ti, Zr and  
5 Hf,  $R^5$  represents a  $C_{1-6}$  linear or branched alkyl group, X represents a Cl or F atom and  
the index n represents an integer from 1 to 3. Preferably, M represents Ti(IV) or Zr(IV),  
 $R^5$  represents a linear or branched  $C_{1-4}$  linear or branched alkyl group, X represents a Cl  
atom and the index n represents 2 or 3.

The use of a mixture of metal complexes of formula (IV) is also convenient,  
10 especially if the catalyst is synthesized *in situ*, and without purification, prior to its use in  
the process.

The co-ingredient of the catalytic system is an alkyl or aromatic carboxylic acid  
anhydride containing 1 to 10 carbon atoms,  $BF_3$  or an anhydrous salt selected from the  
group consisting of the sulfates, chlorides and bromides of a metal cation, said metal  
15 cation being selected from the group consisting of  $Li^+$ ,  $Na^+$ ,  $K^+$ ,  $Cs^+$ ,  $Mg^{2+}$ ,  $Ni^{2+}$ ,  $Ca^{2+}$ ,  $Zn^{2+}$   
and  $Fe^{3+}$ . Preferably, the carboxylic anhydride is the acetic or the propionic anhydride and  
the anhydrous salt is an chloride or a bromide of a metal cation selected from the group  
consisting of  $Li^+$ ,  $Mg^{2+}$ ,  $Ca^{2+}$ ,  $Zn^{2+}$  and  $Fe^{3+}$ .

The use of a mixture of two or three co-ingredients is also possible.

20 The metal complex can be added to the reaction medium in a large range of  
concentrations. As non-limiting examples, one can cite catalyst concentrations ranging  
from 0.001 to 0.20 molar equivalents, relative to the molar amount of the starting  
aldehyde (III). Preferably, the catalyst concentration will be comprised between 0.01 and  
0.15 molar equivalents. It goes without saying that the optimum concentration of catalyst  
25 will depend on the nature of the latter and on the desired reaction time.

The co-ingredient can be added to the reaction medium in a large range of  
concentrations. As non-limiting examples, one can cite salt concentrations ranging from  
0.05 to 1.2 molar equivalents, relative the number of moles of the starting aldehyde (III).  
Preferably, the salt concentration will be comprised between 0.15 and 1 molar equivalent.  
30 Yet, in another preferred embodiment the salt concentration will be comprised between  
0.20 and 0.6 molar equivalents. It goes without saying that the optimum concentration of  
the additional agent will depend on the nature of the latter.

The process of the invention can be carried out in the presence or absence of solvent, but in any case it is advantageously performed in anhydrous conditions, wherein by "anhydrous" it is meant here a solvent which has a content in water below 1% by weight, preferably below 0.1%. When a solvent is required, it is possible to use a pure solvent or a mixture of solvents. Said solvent must be chemically compatible with the reaction conditions, i.e. not interfere with the reaction, and not deactivate the catalyst, e.g. a weak or non-coordinating solvent. Preferred solvents for the process of the invention have a boiling point higher than 60°C and are selected from the group consisting of ethers, esters, aromatic solvents, and linear or branched or cyclic hydrocarbons. More preferably, the solvent is toluene or an ether or ester with a boiling point higher than 80°C.

The temperature at which the process of the invention can be carried out is comprised between 60°C and 140°C, preferably between 80°C and 120°C. Of course a person skilled in the art is also able to select the reaction temperature as a function of the melting and boiling point of the starting and final products and/or the possible solvent.

The invention will now be described in further detail by way of the following examples, the temperatures are indicated in degrees centigrade (°C) ; the NMR spectral data were recorded with a 360MHz machine in CDCl<sub>3</sub>, the chemical displacement  $\delta$  are indicated in ppm with respect to the TMS as standard, the coupling constant J are expressed in Hz and all the abbreviations have the usual meaning in the art.

### Example 1

#### Preparation of the metal catalyst solution

A catalytic solution containing the ZrCl<sub>3</sub>(OPr) complex is obtained according to the procedure described in E.V.Vedejs *et al.*, J. Org. Chem., (1988), 53, 1593). The quantities were modified in order to obtain catalytic solution with a concentration of 1.2 mmole of metal per gram of catalytic solution.

A catalytic solution containing the ZrCl<sub>2</sub>(OPr)<sub>2</sub> complex is obtained according to the procedure described in E.V.Vedejs *et al.*, J. Org. Chem., (1988), 53, 1593) but using an

equimolar amount of  $\text{ZrCl}_4$  and of  $\text{Zr}(\text{OPr})_4$ . The quantities were modified in order to obtain catalytic solution with a concentration of 1.2 mmole of metal per gram of catalytic solution.

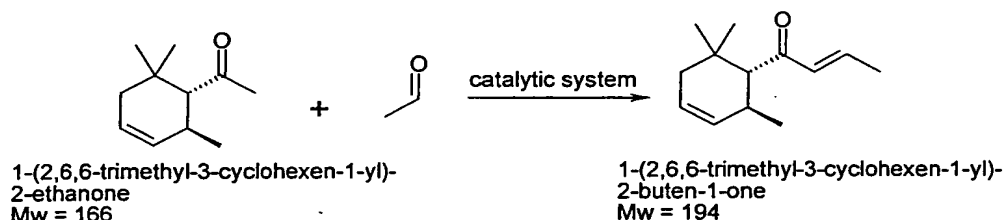
A catalytic solution containing the  $\text{TiCl}_3(\text{O}^i\text{Pr})$  complex is obtained according to the procedure described in E.V.Vedejs *et al.*, J. Org. Chem., (1988), 53, 1593) but using the  $\text{TiCl}_4$  and the  $\text{Ti}(\text{O}^i\text{Pr})_4$  complexes as starting materials. The quantities were modified in order to obtain catalytic solution with a concentration of 1.3 mmole of metal per gram of catalytic solution.

All the resulting solutions were used without further manipulation.

10

General procedure for the preparation of 1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-2-buten-1-one

15



In a 250 ml flask were added 30 g (0.18 mole) of 1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-2-ethanone (94% purity), 12.0 g of butyl acetate, an aliquot according to Table 1 of the catalytic solution as prepared above and a quantity of co-ingredient according to Table 1.

The resulting mixture was stirred at 100°C. To said mixture, 4.0 g (0.09 mole) of acetaldehyde, diluted in 10 g of butyl acetate were introduced under the surface of the liquid, over 3 hours. After the completion of the introduction the reaction was cooled to 35°C. To the cooled reaction medium were added 10 g of acetic acid and then 40 ml of water. After stirring a few minute, the water phase was removed and the organic phase was neutralised by washing it with 25 g of 20% aqueous potassium carbonate.

25

Finally, the butyl acetate was removed by distillation at 130-140°C under ambient pressure and the crude product thus obtained was purified by distillation on a "Vigreux" column to recover the unreacted starting ketone and the final 1-(2,6,6-trimethyl-3-



cyclohexen-1-yl)-2-buten-1-one. The product presented the analytical characteristics described in the literature (i.e. as in US 4,211,242).

Table 1: reaction conditions and yields

5

Run	Metal complex	Catalytic solution Aliquot	Co-ingredient	Co-ingredient quantities	Yields
1	TiCl <sub>3</sub> (O <sup>i</sup> Pr)	3.46 g (0.05 m.e.)	FeCl <sub>3</sub>	2.9 g (0.2 m.e.)	14 %
2	TiCl <sub>3</sub> (O <sup>i</sup> Pr)	3.46 g (0.05 m.e.)	AcOAc	9.18 g (1.0 m.e.)	40 %
3	TiCl <sub>3</sub> (O <sup>i</sup> Pr)	3.46 g (0.05 m.e.)	MgCl <sub>2</sub>	3.8 g (0.4 m.e.)	22 %
4	TiCl <sub>3</sub> (O <sup>i</sup> Pr)	3.46 g (0.05 m.e.)	BF <sub>3</sub>	1.28 g (0.1 m.e.)	16 %
5	ZrCl <sub>3</sub> (OPr)	1.5 g (0.02 m.e.)	MgCl <sub>2</sub>	3.8 g (0.4 m.e.)	45 %
6	ZrCl <sub>2</sub> (OPr) <sub>2</sub>	1.5 g (0.02 m.e.)	MgCl <sub>2</sub>	3.8 g (0.4 m.e.)	32 %

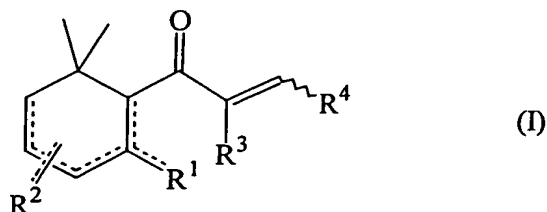
m.e. : molar equivalents relative to the acetaldehyde

AcOAc : acetic anhydride ;      O<sup>i</sup>Pr : OCH(CH<sub>3</sub>)<sub>2</sub> ;      OPr : OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>

Yields are based on the acetaldehyde.

Claims

1. A process for the preparation of a compound of formula



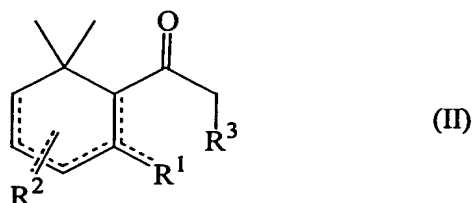
wherein the wavy line indicates that the stereochemistry of the C=C double bond is not defined and the dotted lines indicate a single or a double bond;

R¹ represents a hydrogen atom or a methyl, methylene or ethyl group;

R² represents a hydrogen or a methyl or ethyl group;

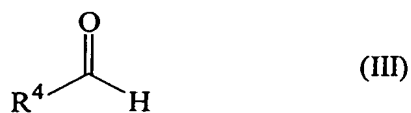
R³ represents a hydrogen atom or a methyl group; and

R⁴ represents a hydrogen atom or a C₁ to C₄ linear or branched alkyl or alkenyl group, characterized in that a starting ketone of formula



wherein R¹ and R² have the same meaning as in formula (I),

is reacted with an aldehyde of formula



wherein R⁴ has the same meaning as in formula (I),

in the presence of a metal complex of formula



in which M is a tetravalent metal cation selected from the group consisting of Ti, Zr and Hf;

R<sup>5</sup> represents a C<sub>1-6</sub> linear or branched alkyl group;

X represents a Cl or F atom; and

5 the index n represents an integer from 1 to 3,

and of a co-ingredient which is an alkyl or aromatic carboxylic acid anhydride containing 1 to 10 carbon atoms, BF<sub>3</sub> or an anhydrous salt selected from the group consisting of the sulfates, chlorides and bromides of a metal cation, said metal cation being selected from the group consisting of Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>, Mg<sup>2+</sup>, Ni<sup>2+</sup>, Ca<sup>2+</sup>, Zn<sup>2+</sup> and Fe<sup>3+</sup>.

10

2. A process according to claim 1, characterized in that R<sup>1</sup> represents a methyl or methylene group;

R<sup>2</sup> represents a hydrogen atom or a methyl group;

R<sup>3</sup> represents a hydrogen atom or a methyl group; and

15 R<sup>4</sup> represents a methyl group.

3. A process according to claim 1, characterized in that the starting aldehyde (III) is acetaldehyde and the ketone (II) is selected from the group consisting of 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1-ethanone, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-1-ethanone, 1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-1-ethanone, 1-(2,6,6-trimethyl-4-cyclohexen-1-yl)-1-ethanone, 1-(6,6-dimethyl-2-methylene-1-cyclohexyl)-1-ethanone, 1-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-1-ethanone and 1-(2,6,6-trimethyl-5-methylene-1-cyclohexyl)-1-ethanone.

25 4. A process according to anyone of claims 1 to 3, characterized in that M represents Ti(IV) or Zr(IV);

R<sup>5</sup> represents a linear or branched C<sub>1-4</sub> alkyl group;

X represents a Cl atom; and

the index n represents 2 or 3.

30

5. A process according to anyone of claims 1 to 5, characterized in that the co-ingredient is the acetic or the propionic anhydride, BF<sub>3</sub>, an anhydrous chloride or bromide of Mg<sup>2+</sup> or Fe<sup>3+</sup> or an anhydrous sulfate of Na<sup>+</sup> or K<sup>+</sup>.

**Abstract**

The invention relates to a process for the preparation of enones by an aldol  
5 condensation of a ketone with an aldehyde in the presence of a novel catalytic system and  
without the pre-formation of an enolate. Said catalytic system comprises a metal complex  
and an ortho-formiate, a carboxylic acid anhydride or an anhydrous salt.

## PCT REQUEST

5510-PCT

Original (for SUBMISSION) - printed on 22.05.2001 02:34:03 PM

0	For receiving Office use only	
0-1	International Application No.	PCT / IB 0 1 / 0 0 9 0 2
0-2	International Filing Date	22 MAY 2001 (22.05.01)
0-3	Name of receiving Office and "PCT International Application"	INTERNATIONAL BUREAU OF WIPO PCT International Application
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.91 (updated 01.01.2001)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	International Bureau of the World Intellectual Property Organization (RO/IB)
0-7	Applicant's or agent's file reference	5510-PCT
I	Title of invention	CATALYTIC ALDOL CONDENSATIONS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
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III-1-6	State of nationality	CH
III-1-7	State of residence	CH

## PCT REQUEST

5510-PCT

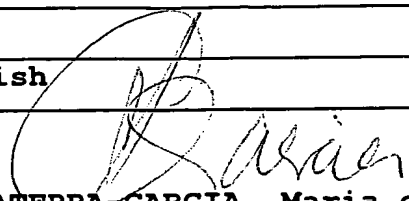
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IV-1	<b>Agent or common representative; or address for correspondence</b> The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	<b>agent</b>	
IV-1-1	Name (LAST, First)	<b>SALVATERRA-GARCIA, Maria de Lurdes</b>	
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V	<b>Designation of States</b>		
V-1	<b>Regional Patent</b> (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	<b>EP: AT BE CH&amp;LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT</b>	
V-2	<b>National Patent</b> (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	<b>IL JP US</b>	
V-5	<b>Precautionary Designation Statement</b> In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	<b>Exclusion(s) from precautionary designations</b>	<b>NONE</b>	
VI	<b>Priority claim</b>	<b>NONE</b>	
VII-1	<b>International Searching Authority Chosen</b>	<b>European Patent Office (EPO) (ISA/EP)</b>	
VIII	<b>Check list</b>	<b>number of sheets</b>	<b>electronic file(s) attached</b>
VIII-1	Request	<b>3</b>	-
VIII-2	Description	<b>6</b>	-
VIII-3	Claims	<b>2</b>	-
VIII-4	Abstract	<b>1</b>	<b>EZABST00.TXT</b>
VIII-5	Drawings	<b>0</b>	-
VIII-7	TOTAL	<b>12</b>	
	<b>Accompanying items</b>	<b>paper document(s) attached</b>	<b>electronic file(s) attached</b>
VIII-8	Fee calculation sheet	<b>✓</b>	-
VIII-16	PCT-EASY diskette	-	<b>diskette</b>

## PCT REQUEST

5510-PCT

Original (for SUBMISSION) - printed on 22.05.2001 02:34:03 PM

VIII-18	Figure of the drawings which should accompany the abstract	
VIII-19	Language of filing of the international application	English
IX-1	Signature of applicant or agent	
IX-1-1	Name (LAST, First)	SALVATERRA-GARCIA, Maria de Lurdes

## FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	22 MAY 2001 (22.05.01)
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

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11-1	Date of receipt of the record copy by the International Bureau	
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